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Magnetic Resonance Imaging-Based Screening for Asymptomatic Brain Tumors: A Review

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Key Words. Brain tumor • Glioblastoma • Screening • Magnetic resonance imaging • Asymptomatic

Abstract

Brain tumors comprise 2% of all cancers but are disproportionately responsible for cancer-related deaths. The 5-year survival rate of glioblastoma, the most common form of malignant brain tumor, is only 4.7%, and the overall 5-year survival rate for any brain tumor is 34.4%. In light of the generally poor clinical outcomes associated with these malignancies, there has been interest in the concept of brain tumor screening through magnetic resonance imaging. Here, we will provide a general overview of the screening principles and brain tumor epidemiology, then highlight the major studies examining brain tumor prevalence in asymptomatic populations in order to assess the potential benefits and drawbacks of screening for brain tumors. ***The Oncologist*** 2019;24:375–384

Implications for Practice: Magnetic resonance imaging (MRI) screening in healthy asymptomatic adults can detect both early gliomas and other benign central nervous system abnormalities. Further research is needed to determine whether MRI will improve overall morbidity and mortality for the screened populations and make screening a worthwhile endeavor.

Introduction

Patients diagnosed with malignant brain tumors have an overall 5-year survival rate of approximately 34.4%, but survival estimates depend on tumor histology; the estimated 5-year survival rate for glioblastoma, the most common malignant brain tumor, is only 4.7% [1]. On the assumption that early detection and treatment can improve survival, investigators are studying ways to identify these neoplasms at a preclinical or early clinical stage. Recently, fluorodeoxyglucose positron electron tomography has been examined as a means of distinguishing between different types of brain tumors [2]. However, magnetic resonance imaging (MRI) is the currently preferred method for the diagnostic evaluation of brain tumors and, therefore, has also been considered a possible tool for the preclinical detection of brain tumors [3].

In this article, we will review the rationale for screening in general, provide a brief overview of brain tumor epidemiology, and evaluate the main studies of the prevalence of various asymptomatic brain tumors in the general population. We will then discuss the benefits and disadvantages of screening for such neoplasms using MRI.

Screening for Disease: Definitions and Rationale

Screening involves the use of a simple, inexpensive test that can be administered to relatively large numbers of asymptomatic individuals in order to identify those likely or unlikely to have the disease. Sensitivity is the probability that a person with the disease will test positive, whereas specificity is the probability that a person without the disease will test negative [4]. Pretest probability refers to the likelihood that an individual will have a particular disease before the results of a diagnostic test are available [4]. In contrast, post-test probability is the likelihood of disease once these results are known [4]. In general, screening is justified if the disease is important to public health, usually because of significant morbidity or mortality, and may be identified at an early or preclinical stage at which reasonable treatment is available and can improve outcomes [5]. A useful screening test should be

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highly sensitive and geared toward a target population with a reasonably high pretest probability of disease. In addition, screening should be cost-effective and acceptable to the target population [5]. However, even when screening meets these criteria, it may have adverse consequences, including financial costs, screening-related morbidity, subsequent clinical workup (in particular for patients with false positive results), and increased anxiety among patients with disease.

The Impact of Various Biases on Screening

The benefits of screening may be limited by various biases, including lead time bias, overdetection bias, selection bias, and length time bias [6].

- Lead time bias is the detection of disease earlier in its natural history than the point at which it would otherwise be diagnosed, without improving overall survival [6]. For example, screening by testing for prostate-specific antigen may detect prostate cancer before symptoms develop, but treatment at that earlier point does not actually prolong survival; it creates the illusion of prolonged survival because it adds the years before clinical detection to the patient's life expectancy [7].
- Overdetection bias involves the discovery of disease, often termed "pseudodisease," that would never become clinically significant for the patient, leading to overtreatment and its side effects [6].
- Selection bias is the identification by screening of a subgroup of patients whose prognosis would be more favorable than average even if they were not screened [6].
- Length time bias, a particularly important type of selection bias, refers to the fact that slower-growing tumors have more opportunities to be detected by screening than rapidly progressive tumors, which become symptomatic before or between screens [5].

From a public policy perspective, cancer screening programs are justified only if they yield an unbiased improvement in cancer-specific mortality and have a favorable cost-benefit ratio.

Epidemiology of and Risk Factors Associated with Brain Tumors

According to the most recent data, the incidence of primary brain tumors in the U.S. is 21.97 per 100,000 persons [1]. Generally speaking, primary brain tumors are more common in whites compared with other groups (e.g., African Americans, Asian Pacific Islanders), and the incidence rates of these malignancies are higher in women than men, owing to the increased prevalence of meningiomas in women [1]. Approximately two-thirds of brain tumors are considered benign or borderline malignant, and the remainder are malignant. Based on their histological features, brain tumors may be categorized as meningiomas, neuroepithelial tumors (ependymal tumors, diffuse astrocytoma, malignant glioma not otherwise specified), tumors of the sellar region, or lymphomas, in order of decreasing frequency [1].

Established primary risk factors include a history of therapeutic radiation, decreased propensity for allergic disease, and factors and genes related to immunity [8]. Ionizing radiation exposure is a well-known risk factor for various brain tumors (meningiomas, gliomas, and acoustic neuromas); elevated incidence rates have been observed among atomic bomb survivors [8]. However, studies of the relationship between dental x-rays or diagnostic procedures and the development of brain tumors have yielded inconsistent results [8]. Head trauma, exposure to nitroso-containing compounds, epilepsy, anticonvulsant use, and cell phone use are also potential but not proven risk factors of concern [8, 9].

Gliomas, the most common malignant primary brain tumors, have estimated age-adjusted incidence rates of 4.67 to 5.63 per 100,000 persons [10, 11]. These tumors are often diagnosed later in life; the median age of diagnosis is 64 years in adults. Most gliomas occur sporadically. Genetic diseases, such as neurofibromatosis, Li-Fraumeni syndrome, and tuberous sclerosis [9], are believed to account for less than 5% of all brain tumors [8].

Materials and Methods

We conducted a systematic search of the literature for studies examining the prevalence of incidental brain MRI findings in asymptomatic adults using MEDLINE via PubMed on November 9, 2017. The following search terms were used: (incidental[All Fields] AND ("brain"[MeSH Terms] OR "brain"[All Fields]) AND ("magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "mri"[All Fields]) AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "findings"[All Fields] OR "diagnosis"[MeSH Terms] OR "findings"[All Fields])). From the search results, articles were excluded on the basis of title and abstract. Additional studies were excluded if they were conducted prior to 2000, if the median age of the sample population was ≥70 years, or if the methods indicated that overtly symptomatic individuals were included as participants. References of the remaining articles were included if they related to brain tumor screening in asymptomatic individuals or addressed the impact of early detection on survival in low-grade gliomas (Fig. 1).

Early Detection of Asymptomatic Brain Tumors: Impacts on Management and Clinical Outcomes

Gliomas

Gliomas are tumors of the supportive glial tissue within the brain parenchyma. The optimal management of low-grade gliomas is controversial; some favor watchful waiting, but others advocate early surgical resection [12–15]. In 2012, a retrospective chart review study evaluated 153 Norwegian patients diagnosed with low-grade gliomas from 1998 to 2009 who were treated at a hospital favoring watchful waiting (region A) or surgical resection (region B) [16]. An early follow-up found an overall survival benefit for patients treated with early surgical resection compared with those managed with biopsy and watchful waiting [16]. Recent follow-up data from this study demonstrated an overall survival benefit in patients treated in region B

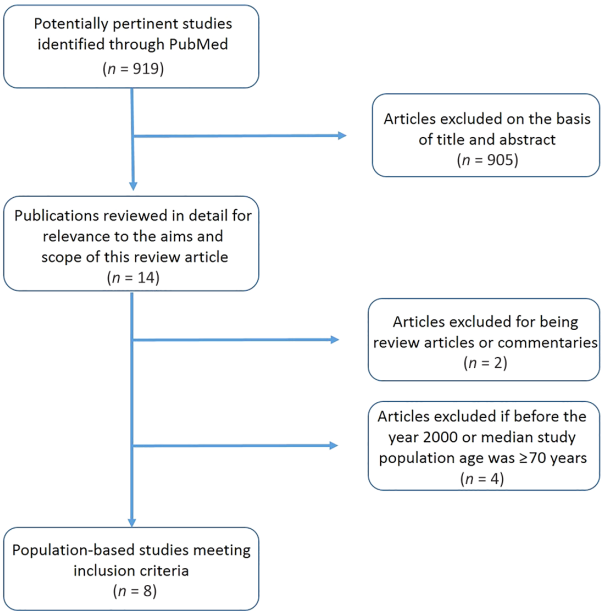

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of population-based studies emphasized in this review article.

versus region A (14.4 years vs. 5.8 years, $p < .01$) [17]. These studies did not evaluate disease-specific survival, but they found that overall survival was similar to disease-specific survival among patients with primary brain tumors (approximate 2% difference) in the Norwegian population [18].

Other studies have identified an association between overall survival and the extent of surgical resection [13, 19]. Specifically, these studies found a higher 5-year overall survival rate among patients who had more extensive surgical resection for their tumors than among patients with less extensive surgery. Furthermore, studies of early preventive surgery for patients with incidentally identified low-grade gliomas suggest that, in centers with specialization in surgical neuro-oncology, the risk of intraoperative seizures is very low; most patients recover successfully and can resume their professional lives without permanent neurological deficits [20–22]. Taken together, these studies support a surgical approach to the management of early gliomas.

However, most gliomas are high grade and incompletely resectable at the time of diagnosis. If screening could identify asymptomatic lesions that could be fully resected, survival with gliomas might improve. The benefit of early detection could also extend to a small subset of patients with secondary high-grade gliomas, which are thought to evolve from low-grade gliomas and account for 5% of all high-grade gliomas [23].

No large-scale studies have evaluated the management and outcomes of low-grade gliomas in completely asymptomatic individuals, but a few studies have examined treatment and survival among patients with low-grade gliomas identified during workup for unrelated symptoms. A recent study by Potts and colleagues demonstrated an overall survival benefit for surgically managed patients with incidentally detected low-grade gliomas compared with similarly managed patients with symptomatic low-grade gliomas, with a mean duration of clinical follow-up of 5.1 years [24]. The authors attributed the benefit to both lower tumor volume and greater extent of resection in the asymptomatic patients. Similarly, Pallud and colleagues reported that patients with incidental low-grade gliomas had better survival than patients with symptomatic low-grade gliomas, independent of their clinical management [25]. Patients with incidental low-grade gliomas were younger at radiologic diagnosis and had smaller tumors, suggesting that incidental gliomas may be precursors of symptomatic gliomas. If so, a brain tumor screening program may offer an overall survival benefit.

Meningiomas

Meningiomas are tumors of the meninges, membranous layers encasing the central and peripheral nervous systems, and represent approximately one third of all brain tumors [26]. These tumors usually follow a benign clinical course but may pose a risk to the patient depending on their anatomical location, initial size, and interval growth. The management of meningiomas depends on tumor size and patient age. Small asymptomatic tumors are often monitored with close clinical follow-up and MRI surveillance [27]. In contrast, large, enlarging, or symptomatic tumors are treated with surgical resection or radiation therapy based on patient preference and whether or not the patient is a good surgical candidate [28]. There has been some interest in early surgical treatment of small asymptomatic meningiomas because they are more likely to permit total resection and may therefore be less likely to recur, and because the surgery has lower complication rates, particularly in younger patients with low surgical risk [29, 30]. However, the median age of diagnosis for meningiomas is 65 years, and studies examining surgical outcomes for small asymptomatic meningiomas in this population consistently report high rates of morbidity ranging from 9.3% to 23.3% [27, 31]. Furthermore, most small asymptomatic meningiomas appear to remain unchanged and asymptomatic over time [32, 33]. Taken together, these studies argue against screening for asymptomatic meningiomas.

Pituitary Adenomas

Pituitary adenomas are benign tumors of the pituitary gland that are classified as functioning or nonfunctioning based on the presence or absence of hormonal hypersecretion. These tumors are further differentiated by size into microadenomas (<1 cm) or macroadenomas (>1 cm). Although many pituitary adenomas are discovered through clinical workup for suspected hyper- or hypopituitarism, a growing number are identified through clinical workup for an unrelated entity. The latter are referred to as “incidentalomas” and may be further subdivided into “micro-incidentalomas” and “macro-incidentalomas.” Much of our knowledge of these tumors is derived from imaging and autopsy studies, both of which suggest that the overwhelming majority (>99%) are micro-incidentalomas [34–37]. Whereas macro-incidentalomas grow at a rate of approximately 12.5% per year, micro-incidentalomas often

grow only 3.3% per year [38]. Their slow growth rate, coupled with the competing morbidity of hypophysectomy, argue against screening for pituitary adenomas.

Acoustic Neuromas

Acoustic neuromas are tumors originating from either the vestibulocochlear or trigeminal nerve. They compose ~10% of all brain tumors and typically present with unilateral sensorineural hearing loss or vestibular symptoms such as vertigo. Prevalence estimates for incidentally discovered acoustic neuromas are based on imaging and autopsy studies and generally range from 0.02% to 1% [39–44]. A recent meta-analysis suggests that acoustic neuromas are generally slow-growing, but their growth rates vary from 0.3 to 4.8 mm per year [45]. The evidence on the relationship between tumor growth rate and hearing loss is mixed; some studies show a better hearing preservation in slow-growing than in rapidly growing tumors, and others identify no association at all [46–49].

Taken together, these data support initial conservative management by radiographic surveillance to characterize the growth rate, with surgery reserved for patients with refractory symptoms, fast growing tumors, or individual preference. The low incidence and slow growth rate of these tumors, as well as the risks of iatrogenic sensorineural hearing loss or vestibular dysfunction, argue against screening for such tumors in the general population.

Comparison of Studies Examining the Prevalence of Asymptomatic Brain Tumors in the General Population

Although some studies have described the prevalence of various types of incidentally discovered brain tumors, few have examined the prevalence of brain tumors in truly asymptomatic populations.

Younger Populations

Two primary large studies have used MRI scans to screen for asymptomatic brain tumors in younger populations. In the late 1990s, Katzman and colleagues studied a population of 1,000 young asymptomatic healthy volunteers at the National Institutes of Health to determine the prevalence of various incidental brain lesions, including brain tumors [50]. The mean age of the participants was 30.6 years; 546 (54.6%) were female and 454 (45.4%) male (Table 1). The volunteers were screened using noncontrast brain MRI to capture T1- and T2-weighted sequences. Board-certified radiologists with additional qualifications in neuroradiology interpreted the images and found that 180 participants (18.0%) had at least one incidental finding. Of these, 151 (15.1%) required no referral, 18 (1.8%) routine referral, and 11 (1.1%) urgent referral. They identified three participants with brain tumors (a low-grade oligodendroglioma, a pilocystic astrocytoma, and an unconfirmed low-grade glioma), all of which required urgent referral. Based on these findings, they estimated the prevalence of primary brain tumors in their healthy asymptomatic population to be 0.2% [50]. Although the authors cited the absence of selection bias as a major strength of the study, the inclusion criteria for "healthy volunteers" were quite strict and may have limited the generalizability of these results.

Weber and colleagues examined 2,536 asymptomatic healthy young men recruited by the German Air Force (mean age 20.5 years), using noncontrast brain MRI to collect both T1- and T2-weighted sequences to detect incidental intracranial abnormalities (Table 1) [51]. Radiologists (but not neuroradiologists) found the overall prevalence of intracranial abnormalities to be 6.6%, including 43 arachnoid cysts (1.7%) and 43 Chiari-I malformation and dystop cerebellar tonsils (1.7%). In addition, they identified five primary brain tumors (one brainstem tumor, two cerebellar tumors, one cerebellopontine angle tumor, and one low-grade glioma), which required urgent referral. Ultimately, they calculated the prevalence of primary brain tumors in their population to be 0.2%, consistent with Katzman's findings [50].

Older Populations

The two major studies examining the prevalence of asymptomatic brain tumors in older populations are the Rotterdam study and the HUNT MRI study [52, 53]. The Rotterdam study was originally designed to identify risk factors for various chronic diseases (cardiovascular, endocrine, respiratory, etc.) in the elderly through imaging of the heart, blood vessels, and other organ systems, as well as collection of body fluid samples for molecular and genetic analyses. The study began in 1990 with 7,983 individuals who were 55 years of age or older. These participants underwent a baseline physical exam and presented for clinical follow-up every 3–4 years. In 1995, the investigators undertook the Rotterdam scan study, a substudy of the parent Rotterdam study, using MRI to examine neurological changes and pathology in the elderly. The Rotterdam study cohort was increased by 3,011 individuals in 2000 and by another 3,932 individuals in 2006 to include people 45 years of age or older, resulting in a total sample of 14,926 individuals. Since 2005, when MRI scanning was officially incorporated into the protocol of the Rotterdam study, nearly one third of the cohort has undergone brain MRI.

In 2007, Vernooij and colleagues published initial findings on incidental brain abnormalities among 2,000 asymptomatic individuals aged 45 years and older (mean age 63.3 years) who were enrolled through the Rotterdam study (Table 1) [54]. Per the Rotterdam scan study protocol, the participants underwent noncontrast brain MRI with T1- and T2-weighted sequences. Residents in neurology and radiology initially interpreted the imaging sequences, but neuroradiologists ultimately reviewed all incidental findings. In total, 145 brain infarcts (7.2%) and 35 aneurysms (1.8%) were identified. They also discovered 31 asymptomatic primary brain tumors (1.6%), of which 18 were meningiomas (0.9%), 6 pituitary adenomas (0.3%), and 4 vestibular schwannomas (0.2%). One participant was tentatively diagnosed with a low-grade glioma, but it was never histologically confirmed. Furthermore, the researchers demonstrated an age-dependent increase in the prevalence of different brain abnormalities, including

Table 1. Overview of design and findings of select population-based studies of asymptomatic brain tumors in the general population

Author (year)	Study design	Number of participants, *n*	Country of origin	Mean age (range), years	Prevalence of primary brain tumors, %	Subdivision of primary brain tumors by type, *n* (%)				
						Meningiomas	Gliomas	Pituitary adenomas	Schwannoma	Other
Katzman et al. (1999) [50]	Cross-sectional descriptive	1,000	United States	30.6 (3.0–83.0)	0.2	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Onizuka et al. (2001) [55]	Cross-sectional descriptive	4,000	Japan	56.0 (24.0–85.0)	0.3	6 (NR)	1 (NR)	3 (NR)	0 (0.0)	1 (NR)
Weber et al. (2006) [51]	Cross-sectional descriptive	2,536	Germany	20.5 (17.0–35.0)	0.2	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vernooij et al. (2007) [54]	Prospective cohort	2,000	The Netherlands	63.3 (46.0–97.0)	1.6	18 (0.9)	1 (<0.1)	6 (0.3)	5 (0.3)	0 (0.0)
Kumar et al. (2008) [56]	Prospective cohort	478	Australia	NR (60.0–64.0)	2.0	3 (0.6)	0	4 (0.8)	0	3 (0.6)
Bos et al. (2016) [52]	Prospective cohort	5,800	The Netherlands	64.9 (NR)	>2.5	143 (2.5)	6 (0.1)	27 (0.5)	8 (0.2)	1 (<0.1)
Haberg et al. (2016) [53]	Prospective cohort	1,006	Norway	59.2 (50.5–66.8)	1.4	10 (1.0)	1 (0.1)	3 (0.3)	1 (0.1)	0 (0.0)

Population-based studies were selected based on the CONSORT flow diagram in Figure 1. Additional information regarding these studies is included within the text.
Abbreviation: NR, not reported.

meningiomas. Vernooij's study sample was drawn from a relatively homogeneous white middle-class population, which may limit its generalizability. However, the study was strengthened by its large sample size of patients 45 years and older.

In 2016, Bos and colleagues published an update on the Rotterdam scan study that included additional clinical follow-up over a 9-year period [52]. A total of 5,800 asymptomatic individuals in The Netherlands (mean age, 64.9 years), including 3,194 (55.1%) women and 2,606 (44.9%) men, had noncontrast brain MRIs with both T1- and T2-weighted sequences (Table 1). In addition, nearly 60% of the participants had at least one follow-up MRI examination, and many had two or more. The team identified 549 participants (9.5%), 306 women (55.7%) and 243 men (44.3%), with at least one brain abnormality. The most commonly identified findings included meningiomas in 143 participants (2.5%) and cerebral aneurysms in 134 participants (2.3%). As other studies have also found, meningiomas were more prevalent in women than in men (Fig. 2); the gender difference is thought to be related to the estrogen and progesterone sensitivity of these tumors [53].

Other asymptomatic brain tumors included 27 pituitary adenomas (0.5%), 6 possible gliomas (0.1%), 8 vestibular schwannomas (0.2%), and 1 pineocytoma (<0.1%). Ninety-one patients with meningiomas (64%) required follow-up with brain MRI; most tumors remained stable in size, but 15 patients (16.5%) were managed surgically based on documented tumor growth on repeat imaging. Most patients with pituitary adenomas were managed with MRI surveillance, but five patients were treated medically and two patients underwent surgery. Ultimately, the authors calculated the prevalence of any brain MRI abnormality in their population to be 9.5%. They did not determine the prevalence of asymptomatic brain tumors but found a 2.5% prevalence of asymptomatic meningiomas alone. The authors concluded that, although asymptomatic brain MRI abnormalities (including brain tumors) are relatively common in the general middle-aged and elderly population, these findings do not usually alter clinical management. Like those of Vernooij's study, the findings of Bos et al. may have limited generalizability because of the ethnic homogeneity of the study population. However, the study's large sample size is a major strength.

In 2016, Haberg and colleagues published findings from the Nord-Trøndelag Health (HUNT) MRI study of asymptomatic brain abnormalities, their clinical consequences, and their clinical outcomes after neurosurgery or radiotherapy in 1,006 participants (median age, 59.2 years), of whom 476 (47.3%) were male and 530 (52.7%) female, in Norway (Table 1) [53]. The investigators found intracranial abnormalities in 242 (24.1%) participants (133 women and 109 men), including 10 meningiomas (1.0%), 3 pituitary tumors (0.3%), 1 vestibular schwannoma (0.1%), and 1 glioma (0.1%), and referred all except one pituitary adenoma to a neurosurgeon. Most of the meningiomas and all of the pituitary tumors were conservatively managed, but the glioma was surgically resected and the vestibular schwannoma was treated with gamma knife radiosurgery. The

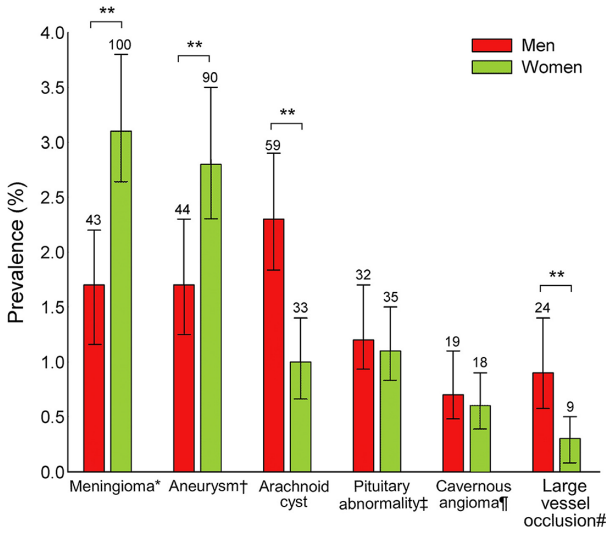

Figure 2. Findings from the Rotterdam scan study, a Netherlands-based prospective cohort study initiated in 1995 to evaluate participants using magnetic resonance imaging (MRI) in order to assess for and identify risk factors of structural intracranial pathology [52]. Bos and colleagues reported on 5,800 individuals with MRI studies to provide prevalence estimates of identified intracranial abnormalities and draw important gender-based comparisons. The bar graph shows the prevalence of the six most common incidental findings on brain MR images in men and women separately. Exact numbers of participants with incidental findings are shown at the top of each bar. Symbols: *, One man and three women had two meningiomas each; †, Four men and five women had two aneurysms each, one woman had three aneurysms, and one woman had four aneurysms; ‡, Possible pituitary adenoma (13 in men and 14 in women) or pituitary cyst (19 in men and 21 in women); ¶, Two women had two cavernous angiomas each, and one man had three cavernous angiomas; #, Lack of flow in the cavernous internal carotid artery (19 in men and 6 in women) or the vertebral artery (five in men, three in women); **, Statistically significant differences ($p < .05$) in prevalence between men and women were found for meningiomas, aneurysms, arachnoid cysts, and large vessel occlusions. Both the figure and its caption have been reproduced with permission from Bos D, Poels MM, Adams HH et al. Prevalence, clinical management, and natural course of incidental findings on brain MR images: The population-based Rotterdam scan study. Radiology 2016;281:507–515 [52]. © RSNA, 2016.

overall prevalence of any intracranial abnormality was determined to be 24.1%, and the prevalence of asymptomatic brain tumors was approximately 1.5%. This prevalence estimate is in agreement with findings from Onizuka et al., who conducted a cross-sectional descriptive study of 4,000 asymptomatic individuals in Japan as part of a large-scale brain disease screening effort using MRI [55]. Haberg's calculations are also consistent with results from the Personality and Total Health Through Life study, a Norway-based cross-sectional study using MRI to determine the prevalence of structural brain abnormalities in 1,006 individuals 60 to 64 years of age [55, 56]. Haberg and colleagues reported a false positive rate of ~2%, primarily attributable to suspected gliomas that were later identified as benign lesions [53]. In spite of this finding, the authors concluded that the clinical benefits of detecting a true positive by neuroimaging would outweigh the harms of a few false

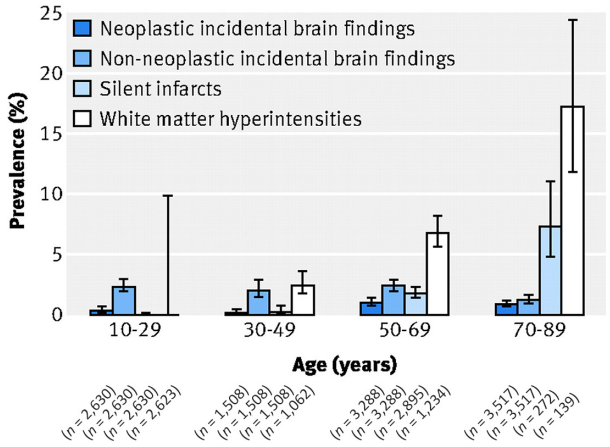

Figure 3. Findings from a meta-analysis of 16 studies (both pediatric and adult) that evaluated participants with magnetic resonance imaging to look for intracranial pathology [57]. The studies included a total of 19,559 individuals and were based in the U.S., Europe, Asia, and Australia [57]. Through their work, Morris and colleagues determined the prevalence of neoplastic and non-neoplastic incidental findings across multiple age groups. This figure has been reproduced from Morris Z, Whiteley WN, Longstreth WT Jr et al. Incidental findings on brain magnetic resonance imaging: Systematic review and meta-analysis. BMJ 2009;339:b3016 [57]. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License.

positives, based on evidence that early intervention for certain intracranial lesions (such as low-grade gliomas) may improve clinical outcomes [16].

Systematic Review and Meta-Analysis of "Incidental" Findings on Brain MRI

In 2009, Morris and colleagues conducted a systematic review and meta-analysis of studies of asymptomatic brain abnormalities detected by brain MRI, in order to estimate the prevalence of such lesions in the general population [57]. Their systematic review incorporated 16 different studies, including those by Katzman et al. 1999, Weber and Knopf et al. 2005, and Vernooij et al. 2007 (but not the study by Bos et al. 2016), for a total of 19,559 individuals, with an age range of 11 to 63 years. The authors found that 137 individuals (0.7%) had an asymptomatic brain tumor. Nearly three-fourths of all brain tumors identified were meningiomas or pituitary adenomas, but 8 (5.9%) were low-grade gliomas. These prevalence estimates are generally consistent with those in the literature (range, 0.2–1.6%; Table 1). The authors also found that the prevalence of asymptomatic brain tumors increased with age (Fig. 3) [54].

Based on the estimate of any incidental finding of 2.7%, Morris and colleagues calculated that the number needed to scan to detect any intracranial abnormality was 37 (Fig. 4) [57]. They further calculated that the number needed to scan for any asymptomatic brain tumor was 143.

Discussion

In this review, we have summarized the major findings from large studies designed to detect asymptomatic brain tumors in the general population and reviewed a few recent studies that offer evidence of a survival advantage for low-grade gliomas identified by MRI. Both the prevalence estimates of primary brain tumors and the clinical benefits of early detection of low-grade gliomas are important considerations for policy makers contemplating a brain tumor screening program. However, one should also recognize the potential selection and lead time biases in many of these observational studies, as noted previously.

In this review, we have outlined the basic principles of screening and described the epidemiology of and risk factors associated with brain tumors. We have also reviewed the findings of large studies designed to detect asymptomatic brain tumors in the general population, and their estimates of the prevalence of these malignancies, a crucial consideration for policy makers contemplating a brain tumor screening program. We also highlighted a few recent studies suggesting that low-grade gliomas, (usually asymptomatic) may be detected by MRI and treated more effectively than high-grade gliomas (generally rapidly progressive), another important consideration for policy on brain tumor screening.

Screening for disease is reasonable if it is cost-effective, acceptable to the target population, and supported by evidence that early intervention improves patient survival or quality of life. In 2014, Mandonnet and colleagues provided a helpful cost–benefit analysis of MRI-based screening for gliomas. Assuming that a screening MRI would cost $150, they calculated that screening 10,000 asymptomatic individuals for brain tumors would cost $1,500,000 and yield four low-grade gliomas [58]. Based on economists' estimates of the value of a person-year at $120,000, the authors concluded that MRI-based screening for brain tumors would be cost-effective if at least 3 years of life were saved through early therapeutic intervention. However, if, as some estimates indicate, brain screening MRI would cost only $70, screening could be cost-effective even if early detection saved only 18 months of life [59]. In a recent survey, 343 (66%) of 390 medical students or members of the European Low-Grade Glioma Network expressed willingness to participate in an MRI screening program for gliomas [60]. These findings argue that MRI-based screening for brain tumors is acceptable to the general population. Early intervention for pituitary adenomas has not been found to improve outcomes, with the possible exception of surgically resectable pituitary macroadenomas, which compose <1% of all pituitary adenomas [61–63]. However, preliminary evidence suggests a survival benefit for patients with surgically managed low-grade gliomas compared with patients with more advanced lesions [16, 24, 25]. Therefore, the discussion of brain tumor screening should focus primarily on gliomas.

The low prevalence of gliomas, the high false-positive rate of brain MRI, and the high cost of screening by MRI argue against screening average-risk populations based on data available at this time. In their systematic review, Morris and colleagues estimated the prevalence of asymptomatic brain tumors to be 0.7% and that of low-grade gliomas much lower [57]. They calculated a number needed to scan of 143 for any asymptomatic brain tumor and 2,000 for gliomas. Moreover, the prevalence of asymptomatic brain abnormalities overall is

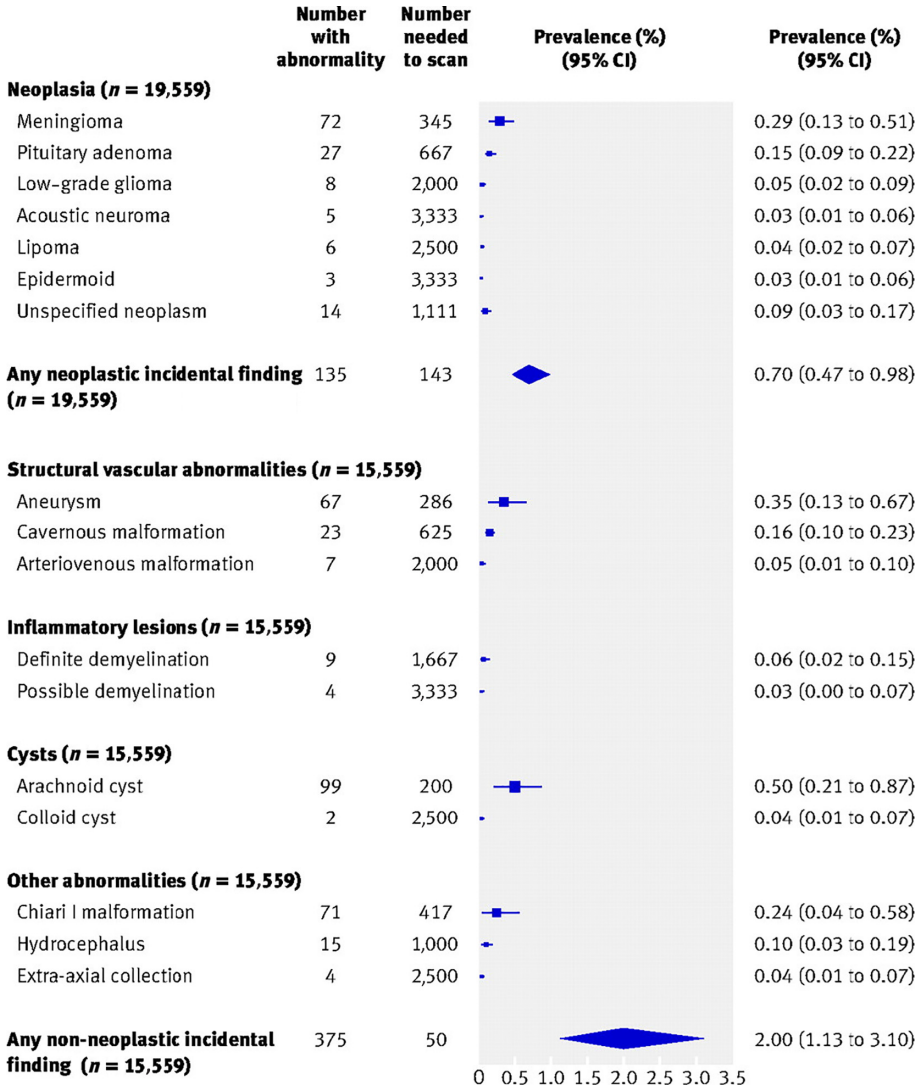

Figure 4. Forest plot from a meta-analysis of 16 studies assessing participants for intracranial abnormalities using MRI [57]. The Forest plot shows the prevalence of neoplastic, vascular, inflammatory and cystic intracranial pathologies. Morris and colleagues provide important estimates of the "number needed to scan" to detect different intracranial abnormalities, a metric that is an essential consideration in the context of brain tumor screening. The figure has been reproduced from Morris Z, Whiteley WN, Longstreth WT Jr et al. Incidental findings on brain magnetic resonance imaging: Systematic review and meta-analysis. BMJ 2009;339: b3016 [57]. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License. Abbreviation: CI, confidence interval.

high, ranging from 6.6 to 24.1%. Thus, screening for gliomas would almost certainly promote overdetection and unnecessary clinical workups for otherwise benign pathology. The low prevalence of brain tumors also contributes to a correspondingly low positive predictive value, which would further limit the yield of brain tumor screening. Other authors have reached similar conclusions [6, 57, 64].

Of course, a key issue is the value of the detection of central nervous system abnormalities other than gliomas. MRI scans detect aneurysms, meningiomas, and all types of vascular abnormalities that are asymptomatic, but does their detection "early" have a positive impact on morbidity or mortality? Our review of the literature on incidentally discovered meningiomas, acoustic neuromas, and pituitary adenomas suggests a limited benefit from early detection, as most of these tumors are small and remain indolent over time. Any future screening program needs to incorporate this question into its evaluation.

Another important consideration is the value of screening in certain high-risk groups, such as patients with neurofibromatosis (NF) type 1 or other genetic syndromes predisposing to brain tumors. A recent retrospective single institution review found that of 826 children aged 1–9 years with NF1 who were screened for optic pathway gliomas (OPGs) using brain MRI [65], 18%, with a median age of approximately 3 years, had an OPG. The authors concluded that MRI-based screening of patients with NF1 could prevent vision loss, noting that 50% of those with visual symptoms at the time of diagnosis experienced eventual vision loss. These findings are consistent with earlier studies reporting similar benefits of MRI-based screening in patients with NF1 [66].

It is entirely possible that MRI-based screening for brain tumors may become feasible in the future. The primary argument against population screening for gliomas is the question of its benefit from a morbidity and mortality point of view. That is the fundamental criterion on which cancer screening programs are premised. Ultimately, because of the biases of screening that were listed previously, it is difficult to ascertain whether a screening test reduces mortality without the conduct of a randomized trial, which has been done for such tests as mammography, sigmoidoscopy and fecal occult blood testing for colorectal cancer, and low-dose CT scanning for lung cancer. Importantly, extensive nonrandomized prospective and retrospective observational studies were conducted prior to undertaking these large expensive randomized trials. Such studies are essential for this question to be fully addressed, and further studies, similar to those reviewed in this paper, are currently underway.

Conclusion

Although the poor prognosis of brain cancers and findings suggestive of a benefit for early detection have generated interest in brain tumor screening, the evidence does not justify MRI-based screening at this time. However, they do support further studies to confirm on a larger scale the potential for the benefits of early detection for brain tumors as a future public health intervention.

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Disclosures

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